

Obsessive-compulsive disorder with bipolar diathesis following isotretinoin therapy remitting upon treatment with olanzapine and fluvoxamine

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Abstract: Isotretinoin, a drug used for moderate to severe acne, has been repeatedly associated with various psychiatric complications, although a definitive causal relationship has not been established to date. This case report describes a 25-year-old male who developed obsessive-compulsive disorder at the age of 23 years following isotretinoin treatment for acne (10–20 mg/day) since the age of 16 years. Although standard treatment for obsessive-compulsive disorder caused mood swings, the combination of fluvoxamine 300 mg/day and olanzapine 15 mg/day significantly improves the clinical picture. Although rare, severe adulthood psychiatric complications may occur following isotretinoin treatment, requiring management which is individually tailored to the patient.

Keywords: isotretinoin, obsessive-compulsive disorder, olanzapine, fluvoxamine, treatment

Introduction

Isotretinoin is a systemic synthetic retinoid used to treat moderate to severe nodulocystic acne vulgaris that is not responding to other therapies, as well as a number of other dermatologic diseases, including psoriasis, hidradenitis suppurativa, ichthyosis, lesions associated with lupus erythematosus, some cases of severe acne rosacea, and various skin cancers, or even adjunctive therapy for acute promyelocytic leukemia.¹

Among other adverse effects, isotretinoin has repeatedly been associated with depression, suicidality, and psychotic symptoms, although the link between isotretinoin use and psychiatric events remains controversial.²

Remarkably, when affective psychosis and obsessive-compulsive disorder (OCD) occur following isotretinoin treatment, associated psychopathology is generally severe and eventually poorly responsive to conventional treatment, as highlighted by recent, large, retrospective studies.³ Also, although patients suffering from bipolar disorder may be at increased risk for mood symptom exacerbations due to isotretinoin therapy, including suicidal ideation, even with a concurrent antimanic therapy,³ less is known about the risk for developing ex novo affective psychosis and antidepressant manic vulnerability when isotretinoin treatment is used during adolescence. Furthermore, acne itself often occurs during adolescence, and can be eventually induced by lithium, a standard treatment for bipolar disorder, which, in turn, usually has its onset at the same age.

Case report

A 25-year-old Caucasian male came to his first psychiatric consultation at the age of 23 years at the suggestion of his general practitioner due to complaints about intrusive

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obsessive thoughts starting about one year earlier. Obsessive symptoms essentially consisted of self-reproachment about his “ineptitude” in sitting academic examinations and consequent overwhelming feelings of guilt toward his parents. There were no associated physical problems, although he reported a history of severe acne vulgaris that had been successfully treated by a dermatologist with isotretinoin 10 mg/day since the age of about 16 years.

Initial evaluation led to a diagnosis of OCD, after excluding a personal or family history for psychiatric disorders. Diagnosis was also made on the basis of the Mini International Neuropsychiatric Interview⁴ and Yale-Brown Obsessive-Compulsive Scale,⁵ the total score for which was 26 (≥ 24 indicates severe OCD). He was prescribed fluvoxamine 100 mg/day, having agreed to the proposal of dose augmentation within the following weeks. Two weeks later he had an unexpected precocious response with a marked ego-dystonic reaction, so current therapy was maintained. More surprisingly, two weeks later, intrusive thoughts reappeared, now associated with loss, concomitant intractable delusions of grandeur, flight of ideas, and an increase in goal-directed activity (eg, a sudden desire to start guitar lessons and to leave law school to become a theatrical agent). A diagnosis of mixed state with psychotic features was made on the basis of a Young Mania Rating Scale⁶ total score of 24 (≥ 12 indicates mania, although mixed state assessment may be roughly estimated). Therapy was then revised, halving the antidepressant dose and adding 1200 mg/day of carbamazepine (lithium, a neuroprotective antisuicidal drug having the potential to worsen psoriasis, and typical antipsychotic augmentation options being disregarded due to a likely lack of compliance and the patient's concerns about potential dermatologic recurrences). Despite the proposal of cognitive behavioral therapy augmentation or other nonpharmacologic interventions, the patient refused to take advantage of any therapy likely to be free of side effects, apparently for compliance reasons. After a further month the patient had a relapse of obsessive symptoms, with a substantial persistence of elation (despite considerably high carbamazepine serum levels, usually increasing by up to 60% in case of fluvoxamine coadministration), so he was prescribed fluvoxamine 25 mg/day and olanzapine 5 mg/day. Doses were then increased every three weeks, reaching a final amount of 300 mg/day and 15 mg/day, respectively. Both obsessive and mood symptoms progressively remitted until almost complete resolution was observed six months later.

Discussion

Patients with OCD and related disorders, eg, body dysmorphic disorder, may have excessive concern about minor variations in skin color or texture, ordinary moles, or thinning hair.⁷ A minority of cases, eg, some patients with severe psychotic body dysmorphic disorder and acne vulgaris, may abuse dermatologic drugs and cosmetics to inhibit normal seborrhea, as in the “Dorian Gray syndrome” (dream of eternal youth), eventually increasing the risk of long-term development of other psychiatric disorders, including affective psychosis.⁸

On the other hand, acne, alopecia areata, atopic dermatitis, and psoriasis may be associated with psychiatric conditions such as depression and suicidal ideation, as well as with the use of some psychotropic medications, possibly suggesting a substantial immunoneuroendocrine overlap.⁹

Nonetheless, when a psychiatric comorbidity is diagnosed, patients seeking dermatologic care may interpret a suggestion to see a psychiatrist as indicating that the dermatologist thinks they are “crazy” or wants to get rid of them, thereby further reducing the chance of appropriate treatment.

Concerning the relationship between isotretinoin and the potential for subsequent onset of psychopathology, positive dechallenge and rechallenge cases have been reported, prompting physicians to look out for the onset or worsening of psychiatric symptoms, including bipolar disorder.^{10,13} Nonetheless, the neurotoxicity of the synthetic retinoic acid analogs is supported by a considerable body of literature.

In fact, retinoids may lead to a decrease in dopaminergic orbitofrontal functioning via their effect on the hippocampus, which modulates dopaminergic function in the medial prefrontal cortex. Retinoic acid-induced deficits in hippocampal function may lead to a downstream effect on orbitofrontal function. However, evidence regarding the effects of retinoic acid in the serotonin pathways is controversial, although higher doses have resulted in decreased or complete loss of serotonergic neurons.¹ This finding has psychiatric implications because the prefrontal dopaminergic imbalance may be closely associated with depression.

Recent evidence from positron emission tomography studies in human subjects showed isotretinoin to be associated with a decrease in orbitofrontal metabolism, which is known to play a major role in the symptomatology of both OCD and bipolar disorder. In fact, the molecular components required for retinoic acid signaling are expressed in the adult brain, and the overlap of brain areas implicated in retinoic acid function, stress, and depression suggests that retinoids

could play a role in affective and anxiety disorders,¹⁴ which are often comorbid.

In this case, the choice of the selective serotonin reuptake inhibitor fluvoxamine was based on its proven efficacy in OCD and on its modulatory effects on σ -1 receptors, which might increase the antipsychotic effect of atypical antipsychotic drugs, possibly contributing to the early psychotic resolution showed by the patient described here.^{15,16} Naturally occurring neurosteroids, as well as many psychotropic drugs, bind to σ -receptors, which may mediate some neuroprotective action, including mood and cognition improvement.^{17,18}

Although olanzapine and other atypical antipsychotic augmentation strategies for selective serotonin reuptake inhibitor-refractory, psychotic OCDs and/or concomitant mood disorder are supported by an increasing body of literature,^{19,20} the choice of a single agent is often difficult.²¹ Given their higher affinity for 5-HT_{2A} receptors than for dopamine receptors, it has been speculated that atypical antipsychotics may induce OCD, even at low doses, due to high 5-HT_{2A} antagonism, whereas improvement is thought to occur only at high doses in response to high dopaminergic antagonism.²²

The choice of olanzapine augmentation for fluvoxamine therapy was also suggested by pharmacokinetic considerations. Fluvoxamine increases the olanzapine plasma concentration by approximately two-fold via CYP1A2 inhibition. On the other side, the alternative strategy of adding carbamazepine (even at low doses) to fluvoxamine and olanzapine was discounted for compliance reasons. Moreover, the patient did not originally show a satisfactory response to this antiepileptic drug even at 1200 mg/day (whereas olanzapine was indeed more effective, especially in reducing psychotic features). There were also pharmacokinetic considerations in the decision not to add carbamazepine, because it increases the renal clearance of olanzapine by about 45% and reduces the half-life of olanzapine by about 20%.²³

In this case, the unusually rapid exacerbation on antidepressants, as well as the presence of plausible iatrogenic-induced depression with flights of ideas,²⁴ pointed to a bipolar diathesis related to previous treatment with isotretinoin, suggesting the switch to an atypical antipsychotic that is associated with a rapid positive antipsychotic response.

Indeed, antidepressant lability could occur even without any previous or current isotretinoin exposure, and it may be difficult to discriminate whether mood switches and rapid exacerbation phenomena are due to isotretinoin or not. It is noteworthy that the patient had no prior familial or personal

predictors of bipolar disorder, including during adolescence, which is the usual age of onset. Moreover, in this case it is remarkable that even a considerable dose of carbamazepine was not able to prevent the mood switch. Also, the use of antidepressants such as fluvoxamine in the course of mixed states is debatable, although they are apparently well established in the management of OCD symptoms.

Although the demonstration of a definitive causal relationship between isotretinoin use and increased risk for subsequent OCD development characterized by iatrogenic vulnerability for affective psychosis is beyond the scope of this report, the modern pathogenic concept of the vulnerability stress model²⁵ (with isotretinoin considered an essential stress factor) of psychiatric disease may prompt further controlled research on this association.

Finally, in addition to the suggestion of a relationship between isotretinoin and psychiatric disorders, this case report suggests that we should consider carefully both the course of illness and psychopharmacologic choices for patients reporting long-term use of isotretinoin during adolescence and complicated by OCD.

Disclosure

The author reports no conflict of interest in this work.

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